

Pivampicillin HCl-probenecid combination in the treatment of uncomplicated gonorrhoea

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A new semisynthetic oral penicillin, pivampicillin HCl, is rapidly hydrolysed to ampicillin in the body. Because of efficient absorption from the gastrointestinal tract, it is reported to give serum concentrations considerably higher than those obtained with a corresponding dose of ampicillin (Frederiksen, Godtfredsen, Nielsen, and Roholt, 1971). A previous study (Förström and Lassus, 1972) showed that, in uncomplicated gonorrhoea, the efficacy of pivampicillin HCl, six capsules of 350 mg. divided into two doses with a 5 to 6-hr interval, is of the same order as that of 2.4 m.u. procaine penicillin. The following trial was performed in order to evaluate the usefulness of a single dose of four capsules of pivampicillin HCl combined with 1 g. probenecid.

Material and methods

The series consisted of 279 males and 91 females with uncomplicated gonorrhoea, diagnosed and treated at the Out-patients Department for Venereal Diseases, University Central Hospital, Helsinki. Specimens for direct microscopy and culture were taken from the urethra of males and from the urethra, cervix, and rectum of females when the patients first attended and at follow-up visits at weekly intervals. The criterion for diagnosis was a positive culture from at least one site. Sensitivity tests to ampicillin and penicillin G *in vitro* were carried out, using the plate-dilution method (Reyn, Korner, and Bentzon, 1958), on all strains isolated, and the inoculation was performed according to the method of Juhlin (1965). Strains with minimum inhibitory concentrations (MIC ≥ 0.2 μ g. ampicillin and ≥ 0.2 i.u. penicillin G per ml. were classified as less sensitive strains. The cultures and sensitivity tests were made at the Department of Serology and Bacteriology, University of Helsinki.

Patients with complicated gonorrhoea were excluded from the study, as were also those with confirmed or suspected hypersensitivity to penicillin, who were treated with doxycycline.

The trial was performed during the period April to December, 1972. The patients were divided into two random groups:

- (1) 180 patients were given four capsules of 350 mg. pivampicillin HCl* (each equivalent to 250 mg. ampicillin) and 1 g. probenecid†;
- (2) The remaining 190 patients received four tablets of 500 mg. ampicillin‡ and 1 g. probenecid.

The capsules and tablets were taken with 100 ml. water in the out-patients clinic. The drugs were given irrespective of meals.

Of the 91 females, 47 (51.6 per cent.) returned for at least two follow-up examinations. Most of the male patients attended for only one follow-up examination.

Re-infection was diagnosed in the cases of those patients who had a positive culture after treatment and who admitted renewed sexual contact with an untreated infected partner.

Results

The overall results are given in the Table. After exclusion of the 112 males (40.2 per cent.) and fifteen

TABLE Overall results of treatment with 1.4g. pivampicillin HCl plus probenecid and 2g. ampicillin plus probenecid

Treatment	Result	Sex		Total	
		Male	Female	No.	Per cent.
Pivampicillin-probenecid	Cure	75	37	112	62.2
	Re-infection	5	—	5 ^a	2.8
	Treatment failure	2	1	3 ^b	1.7
	No follow-up	52	8	60	33.3
	Total	134	46	180	100.0
Ampicillin-probenecid	Cure	77	35	112	58.9
	Re-infection	3	2	5 ^a	2.6
	Treatment failure	5	1	6 ^c	3.2
	No follow-up	60	7	67	35.3
	Total	145	45	190	100.0

^aAll diagnosed more than 1 week after treatment

^bAll diagnosed in the first week

^cThree diagnosed in the first week

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*Pondocillin®, Løvens Kemiske Fabrik, Copenhagen

†Probecid,® Astra Läkemedel AB, Sweden

‡Doktacillin®, Astra Läkemedel AB, Sweden

females (16.5 per cent.) who did not attend at all after treatment, the failure rate among those followed was 2.5 per cent. in the pivampicillin-probenecid group and 4.9 per cent. in the ampicillin-probenecid group. The difference is not statistically significant (χ^2 test; $P > 0.05$).

The proportion of patients not returning for follow-up examinations was similar in the two treatment groups. Of these 127 patients, 25 (19.7 per cent.) harboured strains less sensitive to ampicillin, and 34 (26.8 per cent.) strains less sensitive to penicillin G. The corresponding numbers for the 243 patients attending for follow-up examination were 62 (25.5 per cent.) and 79 (32.5 per cent.) respectively. There was no significant difference in this respect between the two treatment groups. This finding suggests that, in the group of patients not returning for post-treatment examination, the cure rate would be at least as high as in those who were followed.

Strains less sensitive to penicillin were found in sixty of the 180 patients treated with pivampicillin-probenecid (33.3 per cent.) and in 53 of the 190 patients treated with ampicillin-probenecid (27.9 per cent.). The corresponding numbers of strains less sensitive to ampicillin were forty (22.2 per cent.) and 47 (24.7 per cent.) respectively.

Of the 91 females, 38 had positive cultures from rectal specimens before treatment, and in two of these patients the organism was isolated from the rectum only. Of the 38 patients with rectal gonorrhoea, nineteen were treated with pivampicillin-probenecid and nineteen with ampicillin-probenecid. Recurrences were seen in one patient in each treatment group. In the pivampicillin group the recurrence was classed as a treatment failure and in the ampicillin group as a re-infection. Three of the pivampicillin-treated patients and five of the ampicillin-treated patients did not return for post-treatment examination.

No untoward reactions due to the treatment were seen in this series.

Before this study 4×350 mg. pivampicillin HCl was tried as a single dose without probenecid. The result was unsatisfactory; of 87 patients attending for post-treatment examinations, thirteen (14.9 per cent.) had positive cultures for gonococci. There were nine (15.3 per cent.) failures among the 59 males and four (14.3 per cent.) among the 28 females. All of thirteen women who also had rectal gonorrhoea had negative rectal cultures after treatment.

Conclusions

Extensive studies (Eriksson, 1970a, b) have shown that 2 g. ampicillin given in two 1 g. doses with a 5-hour interval without probenecid or in a single

dose combined with 1 g. probenecid, is an effective drug in the treatment of gonorrhoea. A previous study (Forström and Lassus, 1972) showed the efficacy of 2.1 g. pivampicillin HCl (equivalent to 1.5 g. of ampicillin), divided into two equal doses with a 5- to 6-hr interval. The present study shows that a combination of 1.4 g. pivampicillin HCl with 1 g. probenecid in a single dose is another oral alternative, especially for patients who are thought to be unlikely to take the second dose. The same single dose of pivampicillin HCl without probenecid gave unsatisfactory results and should therefore not be used.

Although it is well known that adverse reactions may occur during ampicillin treatment and that probenecid may enhance this risk, no such untoward reactions were seen in this series.

Summary

A clinical trial of pivampicillin HCl, four capsules of 350 mg. (each equivalent to 250 mg. ampicillin) in a single dose combined with 1 g. probenecid, was carried out on 134 males and 46 females with uncomplicated gonorrhoea. In the 120 patients returning for follow-up tests, treatment failure occurred in 2.5 per cent. In a control group of 145 males and 45 females treated during the same period with ampicillin, four tablets of 500 mg. in a single dose combined with 1 g. probenecid, the failure rate was 4.9 per cent. The difference is not statistically significant. Although both ampicillin, to which pivampicillin is hydrolysed in the body, and probenecid may produce adverse reactions, no such reactions were seen in this series. It is concluded that a pivampicillin-probenecid combination in the doses used in the present study is another oral alternative for treatment of uncomplicated gonorrhoea. The same single dose of pivampicillin without probenecid gave unsatisfactory results.

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L'association HCl de pivampicillin et de probénécide dans le traitement de la gonococcie non compliquée

SOMMAIRE

On conduisit un essai clinique de l'HCl de pivampicillin, 4 capsules de 350 mg (équivalant chacune à 250 mg

d'ampicilline) en dose unique, associée à 1g de probénécide, chez 134 hommes et 46 femmes atteints de gonococcie non compliquée. Il y eut 2,5 pour cent d'échecs thérapeutiques parmi les 120 malades revenus pour les tests de surveillance. Dans un groupe de contrôle de 145 hommes et 45 femmes, traités pendant la même période avec l'ampicilline, 4 comprimés de 500 mg en dose unique associée à 1 g de probénécide, il y eut 4,9 pour cent d'échecs. La différence n'est pas statistique-

ment significative. Dans l'organisme, la pivampicillin est hydrolysée en ampicilline: quoique, et l'ampicilline et le probénécide puissent donner des incidents, aucun ne fut observé dans cette série. On conclut que l'association pivampicillin-probénécide aux doses utilisées dans la présente étude, constitue une autre variante orale de traitement de la gonococcie non compliquée. La même dose unique de pivampicillin sans probénécide a donné des résultats non satisfaisants.